Efficacy of adjuvant therapy in patients (pts) with AJCC v8 stage IIIA cutaneous melanoma.

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Background

- Patients (pts) with resected American Joint Committee on Cancer version 8 (AJCC v8) stage IIIA cutaneous melanoma have been under-represented in clinical trials of adjuvant drug therapy.[1-3]
- Anti programmed death 1 (PD1) antibodies and BRAF/MEK-targeted therapy (TT) are approved for adjuvant management of stage III A-D melanoma.
- The risk-benefit ratio of adjuvant drug therapy in stage IIIA melanoma is unclear.
- We examined the risks and benefits of adjuvant drug therapy in pts with AJCC v8 stage IIIA melanoma.

Methods

- In this retrospective, multicenter study, pts with stage IIIA melanoma (AJCC v8) diagnosed between 1 January 2018 and 1 July 2021 who received adjuvant pembrolizumab or nivolumab (PD1), BRAF/MEK-targeted therapy dabrafenib + trametinib, or no adjuvant treatment (OBS) were included.
- Recurrence-free survival (RFS), distant metastasis-free survival (DMFS), and toxicity rates were examined.

Results

- 628 pts from 35 centers across Australia, Europe and USA were included.
- Median follow-up - 2.6 years (IQR, 1.6-3.4 years).
- There were 256 pts in PD1 cohort, 80 in TT cohort and 292 in OBS cohort.
- Rate of completion of PD1 and TT therapy were 57.0% and 70.0% respectively.

Conclusions

- Prognosis in stage IIIA cutaneous melanoma is favourable.
- Adjuvant PD1 or BRAF/MEK inhibitor targeted therapy did not significantly improve recurrence-free survival or distant metastasis-free survival compared to observation in patients with resected stage IIIA melanoma.
- Outcomes after adjuvant therapy in this population needs further study in prospective randomised trials with longer follow-up.

Results

Table 1. Baseline patient characteristics and the median follow-up for the population stratified by adjuvant management.

	PD1, n=256	TT, n=80	OBS, n=292
Sex, n (%)			
Male	150 (58.6)	36 (45.0)	151 (51.7)
Age, median (years) (IQR)	54 (42-64)	49 (37-58)	58 (46-68)
ECOG performance status, n (%)			
0	229 (89.5)	61 (90.0)	258 (88.3)
Melanoma subtype, n (%)			
Superficial spreading	163 (63.7)	41 (63.8)	191 (65.4)
Nodular	40 (15.6)	8 (12.5)	29 (9.9)
Lentigo maligna	6 (2.3)	2 (2.5)	6 (2.1)
Acral lentiginous	9 (3.5)	2 (3.7)	5 (1.7)
Breslow thickness (mm) (IQR)	1.3 (1.1-1.7)	1.3 (1.1-1.5)	1.3 (1.1-1.6)
Mitotic rate, median (per mm^2) (IQR)	3.0 (1.0-5.0)	2.5 (1.0-4.0)	2.0 (1.0-4.0)
Presence of ulceration, n (%)			
Yes	22 (8.6)	3 (3.8)	8 (2.7)
Lymph node involvement, n (%)			
N1a	206 (80.5)	64 (80.0)	253 (86.6)
N2a	50 (19.5)	16 (20.0)	39 (13.4)
Total number of lymph nodes examined, median, n, (IQR)	2 (1.0-3.0)	2 (1.0-2.0)	2 (1.0-3.0)
Maximum diameter of the largest nodal metastasis, median (mm) (IQR)	1.2 (0.5-2.0)	1.0 (0.3-2.0)	0.5 (0.1-1.1)
Complete lymph node dissection, n (%)			
Yes	55 (21.5)	4 (5.0)	24 (8.2)
Extranodal extension, n (%)			
Yes	8 (3.1)	2 (2.5)	3 (1.0)
Mutation status, n (%)			
BRAF wildtype	95 (37.1)	0	41 (14.1)
BRAF V600	87 (37.1)	80 (100)	97 (33.2)
Follow-up, median (years) (IQR)	2.7 (1.7-3.4)	2.4 (1.5-3.2)	2.6 (1.5-3.4)

PD-1, anti-programmed death 1; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; OBS, observation; TT, targeted therapy.

Figure 1. Kaplan Meier curves showing **A. recurrence-free survival (RFS)** and **B. distant metastasis-free survival (DMFS)** by treatment cohorts.

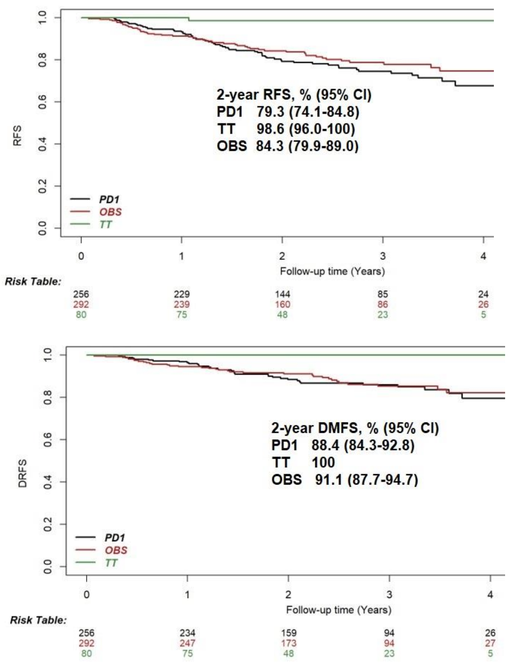

Table 2. Association between clinicopathological characteristics and recurrence within patients treated with immunotherapy (PD1) and observation (OBS).

Variable	PD1		OBS	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.01 (0.99 – 1.02)	0.521	1.04 (1.02 – 1.07)	<0.001
Mitotic rate (per 1/mm^2)	1.07 (1.00 – 1.14)	0.039	1.09 (1.03 – 1.16)	0.003
Breslow thickness (per mm)	1.90 (1.50 – 2.40)	<0.001	1.88 (1.29 – 2.72)	<0.001
Complete lymph node dissection (yes vs. no)	1.81 (1.04 – 3.14)	0.034	2.01 (0.96 – 4.21)	0.065
ECOG performance status (0 vs. 1)	1.04 (0.38 – 2.87)	0.942	1.88 (0.88 – 4.00)	0.101
Groin nodal metastasis (yes vs. no)	1.14 (0.64 – 2.01)	0.663	1.87 (0.97 – 3.62)	0.061
Neck nodal metastasis (yes vs. no)	1.17 (0.51 – 2.68)	0.716	3.82 (1.91 – 7.66)	<0.001

CI, confidence interval; HR, hazard ratio; PD1, anti-programmed death 1; OBS, observation.

Table 3. Landmark survival outcomes stratified by **A. Treatment** and **B. *BRAF* status.**

TABLE 3A	1-year		2-year	
	RFS, % (95% CI)	DMFS, % (95% CI)	RFS, % (95% CI)	DMFS, % (95% CI)
PD-1	93.3 (90.3 – 96.4)	96.4 (94.2 – 98.8)	79.3 (74.1 – 84.8)	88.4 (84.3 – 92.8)
TT	100	100	98.6 (96.0 – 100)	100
OBS	91.3 (88.1 – 94.7)	94.6 (91.9 – 97.3)	84.3 (79.9 – 89.0)	91.1 (87.7 – 94.7)

TABLE 3B	*BRAF* wildtype				*BRAF* mutant			
	1-year RFS, % (95% CI)	1-year DMFS, % (95% CI)	2-year RFS, % (95% CI)	2-year DMFS, % (95% CI)	1-year RFS, % (95% CI)	1-year DMFS, % (95% CI)	2-year RFS, % (95% CI)	2-year DMFS, % (95% CI)
PD-1	94.7 (85.2 – 100)	94.7 (85.2 – 100)	64.5 (43.4 – 95.9)	94.7 (85.2 – 100)	91.4 (85.9 – 97.3)	94.6 (90.2 - 99.3)	71.6 (62.5 – 82.1)	83.5 (75.9 – 91.9)
TT	-	-	-	-	100	100	98.5 (95.6 – 100)	100
OBS	83.0 (67.1 – 100)	88.5 (74.8 – 100)	76.6 (58.8 – 99.7)	88.5 (74.8 – 100)	89.6 (83.7 – 95.9)	92.7 (87.7 – 98.1)	83.4 (76.0 – 91.5)	90.2 (84.2 – 96.5)

CI, confidence interval; DMFS, distant metastasis-free survival; OBS, observation; PD1, anti-programmed death 1; RFS, recurrence-free survival; TT, targeted therapy.

Table 4. Treatment related adverse events.

Toxicity	PD1, n=256		TT, n=80	
	Any Grade, n (%)	≥ Grade 3, n (%)	Any Grade, n (%)	≥ Grade 3, n (%)
Any	136 (53.1)	28 (10.9)	62 (77.5)	14 (17.5)
Cutaneous reaction	27 (10.5)	4 (1.6)	17 (21.2)	0
Fever	2 (0.8)	0	31 (38.8)	8 (10.0)
Endocrinopathies	45 (17.6)	9 (3.5)	1 (1.2)	1 (1.2)
Gastrointestinal	15 (5.8)	5 (1.9)	3 (3.7)	1 (1.2)
Hepatitis	15 (5.8)	6 (2.3)	5 (6.3)	3 (3.8)
Rheumatological	23 (9.0)	3 (1.2)	3 (3.8)	1 (1.2)
Pneumonitis	2 (0.8)	0	0	0
Nephritis	1 (0.4)	0	2 (2.5)	0
Creatine kinase elevation	4 (1.6)	1 (0.4)	0	0
Neurological	2 (0.8)	0	0	0
Haematological	0	0	0	0
Toxicity leading to discontinuation	34 (13.3)		17 (21.2)	
Unresolved toxicity	69 (26.9)		10 (12.5)	

PD1, anti-programmed death 1; TT, targeted therapy.

References

1. Eggermont, A *et al.* NEJM, 2018.
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